COVID-19 Evidence Accelerator Collaborative

Lab Meeting #12

Thursday, July 9, 2020, 3:00-4:00 pm ET

Call Summary

Introduction to Lab Meeting 12

> *"Reliable information is the best weapon we have against Covid-19."*
> *-Charlie Warzel, NYT Opinion, April 3, 2020*

The theme of this week's lab meeting was "learning from our work" or, more specifically, extracting learnings from the Evidence Accelerator's experience conducting its first collaborative parallel analysis, which examined the impact of hydroxychloroquine (HCQ) on patients with COVID-19. In addition to answering key questions about HCQ, this first parallel analysis identified key data variables for studying COVID-19 patients, characterized collective methodological challenges and solutions, and informed best practices for bringing together a diverse group of stakeholders to answer COVID-19 questions in parallel.

A presentation was given by Amy Abernethy, Food & Drug Administration Principal Deputy Commissioner, and the pioneering organizations involved in the first parallel analysis effort: Aetion, COTA, Dascena, HealthCatalyst, Syapse, and TriNetX + Gilead. This presentation was divided into four parts:

1. Defining the Project
2. Describing Populations
3. Describing the Unadjusted HCQ+ Analysis
4. Describing the Adjusted HCQ+ Analysis

Following this presentation, members of the Accelerator community discussed principles for trustworthy real-world evidence generation, which were drafted based on learnings from the first analysis project and the lab meeting discussions to help guide the Accelerator moving forward.

Lab Meeting Presentation

Defining the Project

- The first parallel analysis project was launched on May 20 with the broad goal of understanding how RWD can improve our initial understanding for therapies used for COVID-19.
- More specifically, the first analysis sought to describe patient characteristics and outcomes for hospitalized patients with COVID-19 receiving HCQ alone or with azithromycin:
    - Characterize COVID-19 patient populations at baseline and by treatment with hydroxychloroquine +/- azithromycin
    - Characterize hydroxychloroquine +/- azithromycin treatment (e.g. timing in COVID-19 illness trajectory; monotherapy vs. co-prescription; dose)
    - Characterize safety signals with hydroxychloroquine +/- azithromycin, including subpopulations (e.g. age, diabetes, COPD)
    - Descriptive comparison of clinical outcomes of hydroxychloroquine +/- azithromycin vs. control (supportive treatment only) on key outcomes
- These objectives were intended to provide a descriptive understanding of how hospitalized COVID-19 patients receiving different treatments may compare to one another.
    - Given HCQ's relevance at the time of project launch, it was identified as the first candidate drug to be studied by the Accelerator.
- The parallel analysis project brought together six diverse founding partners to perform the first analysis, each of which has its own unique dataset which warrants unique considerations.
    - Aetion, for example, uses HealthVerity Medical data and pharmacy claims and hospital chargemaster information. Their deidentified linking algorithm captures patients that have both outpatient and inpatient data.
- Despite the notable differences in data sources and the considerations these differences mandated, the parallel analysis project was able to establish a framework for answering the question of interest that could be broadly applied and rapidly adopted by partners.
    - Dascena, for example, joined the parallel analysis project in early June (later in the project timeline than other partner organizations) and was able to rapidly adopt the common protocol for presentation of data at the June 30 parallel analysis meeting.

Describing Populations

- Inclusion criteria for the project varied by partner to accommodate for differences in the partner datasets.
    - Transparency about these differences is key for understanding project findings and communicating these findings to broader audiences.
- In addition, the data collection period varied by partner to accommodate for differences in datasets. These data collections spanned from January to June and may warrant further thought about how the underlying patient population may differ over time.
- This data collection yielded a total population of over 20,000 patients across data sources, many of which received HCQ either alone or in combination with azithromycin.
- For example, broad trends in the patient population demographics from the Syapse dataset, which is derived primarily from urban midwestern populations, demonstrate:
    - The population of patients hospitalized with COVID-19 tends to be older.
    - As age increases, patients are more likely to receive HCQ either alone or in combination with azithromycin.

- Non-Hispanic Black people accounted for a disproportionate number of patients hospitalized with COVID-19 in this region.
- Hospitalized Non-Hispanic Black COVID-19 patients and COVID-19 patients from lower socioeconomic backgrounds were disproportionately represented as having received a treatment for their disease.

Describing the Unadjusted HCQ + Analysis

- As noted in the first objective, parallel analysis project partners were interested in characterizing their COVID-19 patient populations.
- In COTA's patient population, for example, it was demonstrated that a higher proportion of comorbidities/pre-existing conditions were observed within the cohorts receiving HCQ alone or in combination with azithromycin highlighting that, within their cohort, sicker patients received HCQ treatment.
- In the TriNetX + Gilead patient population, patients receiving HCQ were more likely to be receiving supplemental oxygen compared to patients receiving no treatment.

Describing the Adjusted HCQ + Analysis

- Parallel analysis partners used a variety of analytic approaches for the adjusted analysis: propensity score matching, risk set sampling, multivariate analysis, and inverse probability of treatment weighting.
- HealthCatalyst, for example, expressed concern about confounding in their dataset, specifically as it related to whether the outcome of survival was treated as a binary outcome versus a time-to-event endpoint.
- Broad trends in the preliminary findings from the adjusted HCQ+ analysis demonstrate:
    - In general, total adverse event frequency for HCQ alone or in combination with azithromycin was the same as the control.
    - Findings for non-mortality directional outcomes such as discharge from hospital or risk of mechanical were mixed and warrant further investigation.
    - Most groups observed no difference between HCQ containing regimens and the control as it relates to survival. One group found that the survival of patients receiving HCQ containing regimens was worse than those patients receiving the control.

<u>Proposed Accelerator Guiding Principles</u>

The Evidence Accelerator proposes the following nine draft principles for guiding its future parallel analysis work. ***Feedback on these principles from the Accelerator community is welcomed.***

Draft Principles

1. Respect for **patient privacy**
2. **Act fast**, traceability and provenance—understand data generation, processing, curation, and analytics
3. **Transparency**, ruthless transparency
4. **Traceability and provenance**—understand data generation, processing, curation, and analytics
5. **Sharing**—show processes, explore limitations, pitfalls, and celebrate successes—bring work and learnings to the community

6. **Build trust**—show processes. Show curation approaches. Show comparisons. Curation is expensive and takes time, many “eyes” along the way, yields turst, understanding, and confidence in the results
7. Embrace **convergence and discordance** to facilitate understanding
8. Learning is **additive, and continuously integrated** to improve knowledge and understanding
9. **Dissemination**—responsible evidence generation (show what good looks like)